REMARKS

Amendments to the Claims

Claims 1-102 were pending.

Claims 1-51, 56, 59-65, 93 and 95-102 have been cancelled without prejudice to their reinstatement in this or a continuing application.

Claims 52-57, 66-71, 73, 80, 82, 92 and 94 have been amended to depend from Claim 103 or recite limitations of Claim 103.

New Claims 103-134 have been added.

Claim 103 finds support from original Claims 1 and 30.

Claim 104 finds support from original Claim 33.

Claim 105 finds support from original Claim 36.

Claim 106 finds support from original Claims 1, 3 and 30.

Claim 107 finds support from original Claims 1, 7 and 30.

Claim 108 finds support from original Claims 1, 8 and 30.

Claim 109 finds support from original Claims 1 and 12.

Claim 110 finds support from original Claims 1 and 12.

Claim 111 finds support from original Claims 1 and 13.

Claim 112 finds support from original Claims 1 and 13.

Claims 113 and 114 find support from original Claims 1 and 15.

Claim 115 finds support from original Claims 1 and 22.

Claims 116 and 117 find support from original Claims 1 and 21.

Claim 118 finds support from original Claims 1, 17 and 22.

Claim 119 finds support from original Claim 47.

Claim 120 finds support from original Claim 48.

Claim 121 finds support from original Claim 49.

Claim 122 finds support from original Claim 50.

Claim 123 finds support from original Claim 51.

Claim 124 finds support from original Claim 59.

Claim 125 finds support from original Claim 61.

Claim 126 finds support from original Claim 62.

Claim 127 finds support from original Claim 63.

Claim 128 finds support from original Claim 64.

Claim 129 finds support from original Claim 65.

Claim 130 finds support from original Claim 93.

Claim 131 finds support from original Claims 1 and 23.

Claim 132 finds support from original Claims 1, 9 and 30.

Claim 133 finds support from original Claims 1, 10 and 30.

Claim 134 finds support from original Claims 1, 11 and 30.

New Claims 103, 104, 106-110, 113-115 and 119-134 are readable on the elected species "2F2" antibody, pursuant to Applicants' Reply to the Restriction Requirement filed in the U.S. Patent and Trademark Office on February 11, 2008.

New Claims 105, 111, 112 and 116-118 are directed to the "7D8" antibody. These claims are linked to the elected species *via* new Claim 103. These claims should be examined in the subject application upon a finding of allowable subject matter of the elected species.

It is noted that certain withdrawn claims have been amended to preserve Applicants' right to have the withdrawn process claims rejoined upon a finding of allowable subject matter.

Withdrawn Claims 52-55, drawn to transfectoma and host cells, have been amended to be commensurate in scope to the human monoclonal antibody of Claim 103. Applicants note that these claims were subject to restriction but in view of the fact that they are being amended to the scope of the invention under examination, reconsideration and withdrawal of the restriction requirement with regard to Claims 52-55 are respectfully requested.

Entry of these amendments is respectfully requested.

Supplemental Declaration

Applicants submit herewith an executed Supplemental Declaration by Inventor Jessica Teeling.

Correction of Sequence Listing

Applicants submit concurrently with this Amendment a Request for Correction of Errors in the Sequence Listing Pursuant to 37 C.F.R. § 1.825. Also submitted is a Statement by Dr. Tom Vink in support of Correction of the Sequence Listing. A Second Substitute Sequence Listing is also being submitted herewith to correct obvious errors in the Sequence Listing with regard to SEQ ID NOs:2, 4, 6, 8, 10, 12, 13, 19 and 25, as discussed below.

Specifically, leader sequences, which are typically cleaved off during secretion in cells that produce antibodies, have inadvertently been included in the heavy and light chain variable regions set forth in SEQ ID NOs:2, 4, 6, 8, 10 and 12. It would have been obvious to a person skilled in the art at the earliest priority date of the subject application that the leader sequences had been included. As evidenced by Dr. Vink's Statement, it would have been also obvious to a person skilled in the art at the earliest priority date of the subject application what the actual heavy and light chain variable regions are without the leader sequences.

Furthermore, the V_H CDR1 sequences (*i.e.*, SEQ ID NOs: 13, 19 and 25) of the claimed antibodies erroneously contain an additional amino acid pursuant to the Kabat definition. As supported by Dr. Vink's Statement, it would have been obvious to a person skilled in the art at the earliest priority date of the subject application that an extra amino acid residue is included at the N-terminus in SEQ ID NOs:13, 19 and 25.

As required by 37 C.F.R. § 1.825, Applicants state that no new matter has been added to the Second Substitute Sequence Listing. Entry of the amendments to the Second Substitute Sequence Listing is respectfully requested.

Rejection of Claims 12, 15, 16, 21, 29-33, 41-43, 49, 50, 61 and 64 Under 35 U.S.C. § 112, First Paragraph

Claims 12, 15, 16, 21, 29-33, 41-43, 49, 50, 61 and 64 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

In the present Amendment, Claims 12, 15, 16, 21, 29-33, 41-43, 49, 50, 61 and 64 have been cancelled without prejudice, thus rendering the rejection moot.

New Claim 103 and other claims dependent from Claim 103 are drawn to V_H CDR3 having the amino acid sequence set forth in SEQ ID NO:15. Other claims are defined by the antibody described in new Claim 103 and/or the structural or binding characteristics of, or similar to, the antibody of Claim 103.

Applicants assert that new claims meet the written description requirement for at least the reasons set forth herein.

At the time of the invention, it was well known that the heavy chain CDR3 region plays a significant role in determining the specificity of antibody binding. In the 1990s, well before the priority date of the present patent application, studies were performed to localize the specificity-determining sequences within antibodies and determine their relative contributions to antigen recognition. A number of studies identified the heavy chain CDR3 region as being critical in determining antigen-binding specificity (*see* also page 31, lines 23 to 24 of the present application). It was found that the heavy chain CDR3 sequence not only may be *necessary* for maintaining specificity, but it can be *sufficient* in the sense that a heavy chain CDR3 alone can retain and confer antigen specificity when placed into a different antibody context. This is evidenced by the enclosed references (Barbas *et al.* (1994), Barbas *et al.* (1995) and Ditzel *et al.* (1996); attached hereto as Appendices A, B and C, respectively).

Specifically, Barbas *et al.* (1995) showed that replacement of the heavy chain CDR3 sequence of an anti-tetanus toxoid Fab by heavy chain CDR3 sequences of Fabs specific for human placental DNA resulted in the chimeric molecule being specific for the human placental DNA. A similar result was obtained by Ditzel *et al.* (1996), who replaced a heavy chain CDR3 sequence of a tetanus-toxoid specific Fab by a heavy chain CDR3 sequence of a polyspecific Fab LNA3 and obtained a chimera that could bind to the same antigens as LNA3.

Additional evidence is provided in the enclosed references (Polymenis and Stollar (1994); Klimka *et al.* (2000); Beiboer *et al.* (2000); and Rader *et al.* (1998); attached hereto as Appendices D, E, F and G respectively). In particular, Polymenis and Stollar (1994) showed that a single chain variable fragment (scFv) not capable of binding a specific antigen, Z-DNA, could be converted into a Z-DNA-binding scFv by grafting the heavy chain CDR3 region of a Z-DNA-binding antibody onto it (*see* Fig. 3 therein). Polymenis and Stollar also showed that significant Z-DNA binding was retained even when the heavy chain CDR3 of a functional ZDNA binding

antibody was combined with other heavy chain variable sequences which only had 44% sequence identity with the corresponding sequences of the variable region from which the heavy chain CDR3 region was derived.

Furthermore, Klimka *et al.* describe the production of a humanized anti-CD30 antibody using only the heavy chain variable CDR3 domain, *i.e.*, the major determinant for epitope-specificity, of a murine anti-CD30 antibody, Ki-4. The human version of the murine anti-CD30 antibody was produced by sequentially replacing the murine variable heavy and light chain genes with human V gene repertoires, while retaining only the heavy chain CDR3 domain of the murine Ki-4 antibody (*see* Abstract; page 253, column 1, second full paragraph; and page 255, "Results" section, last paragraph of column 1 - column 2). As demonstrated by Klimka *et al.*, the anti-CD30 antibody was found to compete with the parental murine antibody for binding and to retain other functional characteristics of the parental murine antibody (*e.g.*, inhibits the shedding of the extracellular part of the CD30 receptor from L540 cells). Like Klimka *et al.*, Beiboer *et al.* generated recombinant antibodies using only the heavy chain CDR3 sequence of a parent antibody. Specifically, the authors engineered an antibody to epithelial glycoprotein-2 (EGP-2) by retaining only the murine heavy chain CDR3 domain of the murine MOC-31 antibody. As confirmed in Beiboer *et al.*, "the heavy chain CDR3 is the main loop involved in antigen binding ..." (page 839, left column, last full paragraph). The newly created antibody was found to bind the same epitope and have a similar binding affinity as the parental murine antibody. Similarly, using only the CDR3 sequence of a parent antibody, Rader *et al.* describe the production of a humanized anti-integrin avb3 antibody using the heavy and light chain variable CDR3 domains of the murine anti-integrin avb3 antibody, LM609. Rader *et al.* report that several antibodies were produced having different sequences outside the CDR3 regions and capable of binding the same epitope as the parent murine antibody with affinities as high as or higher than the parent murine antibody.

As evidenced by the foregoing prior art publications, it was well-known in the art at the priority date of the present application that the heavy chain CDR3 alone from an antibody with a given binding specificity can be sufficient to enable the generation of a class of antibodies having the same binding specificity. Therefore, new Clams 103-134 meet the written description requirement.

Rejection of Claims 9, 10, 24, 29 and 61 Under 35 U.S.C. § 112, Second Paragraph

Claims 9, 10, 24, 29 and 61 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of "characteristics" or "derived."

Claims 9, 10, 24, 29 and 61 have been cancelled, thus rendering the rejection moot.

Rejection of Claims 1, 2, 7-11, 22-24, 29, 44, 47, 48, 51, 59, 61-63 and 65 Under 35 U.S.C. § 102(b)

Claims 1, 2, 7-11, 22-24, 29, 44, 47, 48, 51, 59, 61-63 and 65 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Kucherlapati *et al.* (WO 96/33735; hereinafter, "Kucherlapati") as evidenced by Teeling *et al.* (2006). The Office Action stated that: "Teeling *et al.* indicate that all human antiCD20 antibodies inherently bind the epitope recited in claims 23-24 (see abstract). The term "derived" whilst indefinite as per above will be interpreted as having any amino acid in common with the recited sequence." Applicants respectfully disagree with this conclusion, as discussed below.

Kucherlapati discloses methods of producing humanized antibodies from transgenic mice. Kucherlapati teaches that CD20 can be a potential antigen for which such an antibody can be raised using the method described. CD20 is listed among other 180 or so potential targets (*see* Kucherlapati at page 14, line 19 through page 16, line 21 for the entire list of the targets). However, Kucherlapati fails to exemplify an actual antibody that binds CD20, let alone an antibody having the CDR3 sequence set forth in SEQ ID NO:15 or binding and functional properties of the claimed antibody.

Further, the epitopes defined by the claimed antibodies are novel. For example, the chimeric monoclonal antibody, rituximab, used as control in the application, has an epitope different from that of the claimed antibodies (*see* Examples 14 and 15 of the present application). Even 2F2 and 11B8 of the present invention bind to different epitopes (*see* Examples 14 and 15 of the present application).

New Claim 103 and other claims dependent from Claim 103 are drawn to V_H CDR3 having the amino acid sequence set forth in SEQ ID NO:15. Other claims are defined by the antibody described in new Claim 103 and/or the structural or binding characteristics of the

antibody of Claim 103. Because Kucherlapati does not disclose a monoclonal antibody that has the structural and binding properties recited in the claims, new Claims 103-134 are not anticipated by the teachings of Kucherlapati.

Rejection of Claims 1-3, 7-11, 22-24, 29, 44, 47, 48, 51, 59, 61-63, 65 and 93 Under U.S.C. § 103(a)

Claims 1-3, 7-11, 22-24, 29, 44, 47, 48, 51, 59, 61-63, 65 and 93 have been rejected under U.S.C. § 103(a) as being unpatentable over Korman *et al.* (WO 01/14424; hereinafter, "Korman") in view of Kucherlapati.

Korman teaches a method of producing human IgG1 antibodies from transgenic mice. As acknowledged in the Office Action, Korman does not teach or suggest any monoclonal antibody, human or otherwise, that binds to CD20 (*see* Office Action at page 7). Nor does it teach or suggest that V_H comprises a CDR sequence set forth in SEQ ID NO:15.

The teachings and deficiencies of Kucherlapati are discussed above.

As noted above, Claims 1-3, 7-11, 22-24, 29, 44, 47, 48, 51, 59, 61-63, 65 and 93 have been cancelled without prejudice, rendering the rejection moot. New Claim 103 recites that V_H of the claimed antibody comprises CDR3, the amino acid sequence of which is set forth in SEQ ID NO:15.

The claimed invention is not obvious because the combined teachings of Korman and Kucherlapati do not teach or suggest the claimed human monoclonal antibody having the CDR sequence of SEQ ID NO:15 or provide a reasonable expectation of success in arriving at the present invention. Nor was it predictable to one of ordinary skill in the art to create a human monoclonal antibody having the CDR3 sequence of SEQ ID NO:15. This application is the first disclosure and the first exemplification of a human monoclonal antibody that binds to CD20 and has *in vivo* efficacy in the treatment of various types of cancer and inflammatory diseases.

Further, the present invention achieves unexpected results and advantages over prior art antibodies, as exemplified by the commercial antibody rituximab. Applicants have demonstrated the unexpected ability of their antibodies to induce complement dependent cytotoxicity (CDC) of cells expressing CD20 in the Examples of the present application. Specifically, Applicants demonstrated that both 2F2 and 7D8 exhibit superior CDC activity compared to rituximab (*see*

Figure 15 and page 79, line 10 to 18). Furthermore, both 2F2 and 7D8 are effective in mediating CDC of Raji cells which are relatively resistant to complement attack, whilst rituximab does not efficiently lyse these cells (*see* Figure 16 and page 79, lines 20 to 34).

At least for the foregoing reasons, new Claims 103-134 are not obvious over Korman in view of Kucherlapati.

Supplemental Information Disclosure Statement

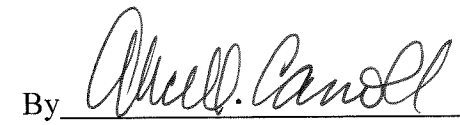
A Supplemental Information Disclosure Statement is being filed concurrently herewith to re-submit certain references which have been lined-out in prior submitted Information Disclosure Statements. Copies of these references are being provided again for the Examiner's convenience. Entry of the Supplemental Information Disclosure Statement is respectfully submitted.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alice O. Carroll
Registration No. 33,542
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: November 3, 2010